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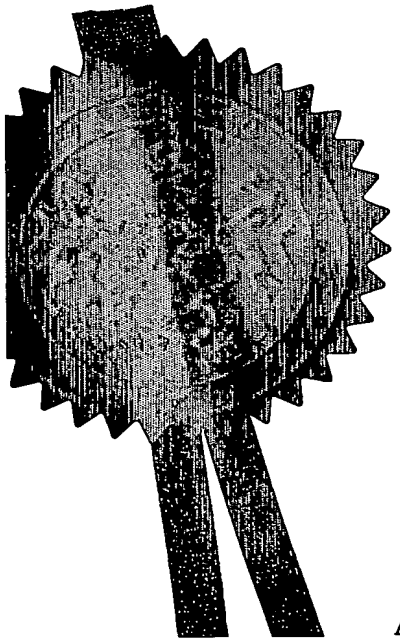

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Dated 30 January 2004

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Request for grant of a patent

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09 JUL 2003

1.	Your reference	G-33005P2/BCK 9936
2.	Patent application number *(The Patent Office will fill in this part)*	0316087.6
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	SANDOZ GMBH BIOCHEMIESTRASSE 10 A-6250 KUNDL, TIROL AUSTRIA
	Patent ADP number *(if you know it)*	86387360001
	If the applicant is a corporate body, give the country/state of its incorporation	AUSTRIA
4.	Title of invention	Organic Compounds
5.	Name of your agent *(If you have one)*	Craig McLean
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	Novartis Pharmaceuticals UK Limited Patents and Trademarks Wimblehurst Road Horsham West Sussex RH12 5AB
	Patents ADP number *(if you know it)*	71815220002

		Country	Priority application number *(if you know it)*	Date of filing (day/month/year)
6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number			

		Number of earlier application	Date of filing (day/month/year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application		

8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes

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Continuation sheets of this form	
Description	11
Claim(s)	2
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	One ✓
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature

Date 9th July 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. S. Schnerr
01403 323069

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Organic Compounds

This invention relates to pharmaceutical compositions of venlafaxine.

Venlafaxine is the non-proprietary name for 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol and is useful in treating a number of disorders including depression, anxiety, panic disorder and pain. Venlafaxine is administered as venlafaxine hydrochloride in treating depression. See The Merck Index, 12th Edition, entry 10079.

Published European patent application EP 797 991 A discloses encapsulated extended release formulations of venlafaxine hydrochloride which comprise a hard gelatin capsule containing spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and hydroxypropylmethylcellulose coated with ethyl cellulose and hydroxypropylmethylcellulose. Solvents used in the coating step include methylene chloride and anhydrous methanol.

The present applicants have sought to overcome the drawbacks of hitherto known formulations of venlafaxine.

In one aspect, therefore, this invention provides coated core pellets comprising venlafaxine for use in a delayed and/or extended release formulation which core pellets undergo at least one coating step in the absence or substantial absence of organic solvents.

In another aspect, this invention provides a coated pellet comprising

a) a pellet core which comprises venlafaxine hydrochloride;

b) a first coating which comprises a lipophilic layer or a sparingly water-soluble layer, and

c) a second coating which comprises a water-soluble or water-insoluble polymer.

The pellet core may comprise in addition a carrier, for example microcrystalline cellulose. The pellet core may comprise in addition a binder, for example a cellulose derivative, e.g. hydroxypropylmethylcellulose (HPMC). The present applicants have found that HPMC of e.g. grade K 4 M has an appropriate viscosity for use in this invention.

The pellet core may be spheroidal in geometry and typically exhibits a diameter, when coated, of between around 0.5 mm to 2 mm, e.g. 0.7 to 1.75mm, for example 0.8 mm to 1.5 mm.

The first coating and second coating may each be complete or substantially complete, e.g. so as to provide a surface coverage of at least 60 %, e.g. 70 % or more, e.g. 80 to 95 % around the core (first coating) or around the first coating (second coating). Complete coatings are preferred.

The first coating may comprise between 0.5 to 5% by weight, e.g. 1 to 4%, of the first-coated pellet core.

The second coating may comprise 8 to 30% by weight, e.g. 10 to 25%, based on the total weight of the double-coated core.

The first coating serves to protect the pellet core from moisture, both in storage and in use.

The lipophilic layer may comprise a fat, fatty alcohol or wax. The lipophilic layer preferably comprises cetostearyl alcohol, castor oil or dibutyl phthalate.

The sparingly water-soluble layer may comprise a carbohydrate or a sugar, e.g. lactose, in the form of an aqueous suspension wherein the concentration of the carbohydrate or sugar is at least about 0.1 g/ml, e.g. 0.15 to 0.25 g/ml or greater, e.g. 0.28 g/ml to 0.4 g/ml or even higher, e.g. 0.41 to 0.6 g/ml, for example 0.43 or 0.5 g/ml.

The sparingly water-soluble layer, which may be formed by spray-coating, may comprise lactose in an amount of up to about 30% to 40% by weight.

The water-soluble or water-insoluble polymer may be selected from acrylate-based aqueous dispersions, ethylcellulose aqueous dispersions and polyvinyl acetate aqueous dispersions. Thus the second coating is aqueous-based and serves to provide the extended release effect.

Water-insoluble polymers are preferred and may serve to control release of the venlafaxine. The water-insoluble polymer may display pH-independent solubility and may comprise a water-insoluble polymer mixture.

The term "water-insoluble", as used herein is understood to mean a polymer solubility in water at room temperature of less than 100 mg/litre, e.g. 20 mg/litre or less, e.g. 10mg/litre or less, e.g. 1mg/litre or less.

In a preferred aspect, the pellet core and/or coating(s) of this invention are free of, or substantially free of, polyvinylpyrrolidone.

In another aspect, this invention provides a composition comprising coated pellets as herein described. The composition may be in tablet, hard gelatine capsule or sachet form.

In another aspect, this invention provides a coated pellet consisting of or consisting essentially of

a) a core containing venlafaxine hydrochloride in an amount of between 30 and 60 % by weight, microcrystalline cellulose in an amount of between 40 and 65% by weight, and HPMC K 4 M in an amount of between 0.3 and 0.8% by weight, wherein the respective weights are in relation to the double-coated core;

b) a first coating containing cetostearyl alcohol in an amount of between 1.0 and 4.0 %, e.g. 1.7 and 3.5 %, by weight of the first-coated pellet core; and

c) a second coating containing an acrylate-based polymer in an amount of between 9 and 25%, e.g. 9 and 13 %, by weight based on the total weight of the double-coated core, and talc

in an amount of between 2 and 15%, e.g. 3 and 8 %, by weight based on the total weight of the double-coated pellet core.

Suitable acrylate-based polymers or water-insoluble polymers having pH-independent solubility are available commercially e.g. from the Röhm company, Germany, under the trade marks EUDRAGIT, SURELEASE or AQUACOAT, e.g. EUDRAGIT NE 30 D, EUDRAGIT RL 30 D, EUDRAGIT RS 30 D or KOLLCOAT SR as dry polymer.

The second coating may further comprise triethyl citrate or dibutyl phthalate, e.g. in an amount of 5 to 35%, e.g. 10 to 30 %, by weight of the dry polymer.

In a further aspect, this invention provides a composition consisting of or consisting essentially of coated pellets as herein described. The composition may be in tablet, hard gelatine capsule or sachet form.

In a further aspect, this invention provides a process for preparing pellets as herein described which comprises the steps of

Ai) forming a pellet core mixture comprising venlafaxine hydrochloride with water or an aqueous solution of a binder,

Aii) extruding and spheronising the mixture, and subsequently drying,

Aiii) applying the first coating,

Aiv) applying the second coating, and subsequently sieving so as to obtain coated pellets within the desired size range,

wherein the process is carried out in the absence or substantial absence of any organic solvent at least in the second layer.

Coating steps Aiii) and Aiv) may employ conventional fluidised bed processes. Alternatively, the first coating layer may be applied using a spray melt process or by using a tangential coating process.

In another embodiment, the first coating layer may be dissolved in an organic solvent medium, e.g. methylene chloride or methanol, and sprayed onto the pellet cores.

In a further aspect, this invention provides a process for preparing pellets as herein described which comprises the steps of

Bi) forming a pellet core mixture comprising venlafaxine hydrochloride, microcrystalline cellulose and HPMC with water or an aqueous solution of a binder,

Bii) extruding and spheronising the mixture, and subsequently drying,

Biii) collecting the core pellets between 0.8 mm to 1.75 mm for further processing,

Biv) applying the first coating, and

Bv) applying the second coating
wherein the process is carried out in the absence or substantial absence of any organic solvent at least in the second layer.

Coating steps Biv) and Bv) may employ conventional fluidised bed processes. Alternatively, the first coating layer may be applied using a spray melt process or by using a tangential coating process.

A preferred embodiment of each of the above processes is such that the process is carried out in the absence or substantial absence of any organic solvent in both the first coating layer and in the second coating layer.

The venlafaxine hydrochloride is sourced from the Medichem company, Spain. The venlafaxine may be used in any polymorphic form, e.g. in the forms known as Form I or Form II. . The compositions of this invention may be administered to adults in doses ranging from 75 mg to 350 mg venlafaxine per day.

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Following is a description by way of example only of compositions of this invention.

Example 1

Pellets according to the following composition are prepared and filled into hard gelatin capsules.

		Quantity per capsule (mg)
I	Core pellets	
	venlafaxine HCl	169.70
	microcrystalline cellulose	199.0
	HPMC K 4 M	1.85
II	Wax coating	
	cetostearyl alcohol	9.26
III	Polymer coating	
	Eudragit NE 30 D	56.97
	talc	28.49
	Total weight of coated pellets	476.90

The core pellets are prepared by mixing the above components with a small amount of water, i.e. enough to form a paste without dissolving the venlafaxine, under I followed by extrusion spheronisation. The wax coating is applied using a fluidised bed process at or close to the melting temperature of the coating layer. The subsequent polymer (sustained release) coat is applied by a fluidised bed process. The resulting coated pellets are sieved so as to obtain a desired pellet size range of between 0.85 mm and 1.75 mm.

Example 2

Pellets are prepared in analogous manner to those in Example 1 with replacement of the wax coating by an aqueous suspension of lactose at a concentration of 0.15 g/ml. The suspension is sprayed onto the cores using a perforated pan or a fluidised bed process.

In view of the small amount of water involved in the first coating step, negligible dissolution of venlafaxine takes place and a protective layer is formed between the pellet core and the second coating.

Example 3a) and 3b)

Pellets according to the following composition are prepared and filled into hard gelatin capsules.

		Quantity per capsule (mg)
I	Core pellets	
	venlafaxine HCl	169.70
	microcrystalline cellulose	193.27
	HPMC K 4 M	1.85
II	Wax coating	
	cetostearyl alcohol	10.03
III	Polymer coating	
	Eudragit NE 30 D	70.10
	talc	35.05
	Total weight of coated pellets	480.00

The core pellets are prepared by mixing the above components with a small amount of water, i.e. enough to form a paste without dissolving the venlafaxine, under I followed by extrusion spheronisation. The pellets with size between 0.8mm and 1.75mm are collected. The wax coating is applied using

in 3a) a fluidised bed process, and

in 3b) tangential coater,

at or close to the melting temperature of the coating layer. The subsequent polymer (sustained release) coat is applied by a fluidised bed process.

Example 4a) and 4b)

Pellets are prepared in analogous manner to those in Example 1 with replacement of the wax coating by an aqueous suspension of lactose at a concentration of 0.43 g/ml. The suspension is sprayed onto the cores using

4a) a perforated pan, or

4b) a fluidised bed process.

In view of the small amount of water involved in the first coating step, negligible dissolution of venlafaxine takes place and a protective first layer is formed between the pellet core and the second coating.

Example 5

A capsule composition is prepared in analogous manner to that in Example 1 with the following component amounts.

		Quantity in %
I	Core pellets	
	venlafaxine HCl	37.3 % by weight of core pellets
	microcrystalline cellulose	62.1 % by weight of core pellets
	HPMC K 4 M	0.5 % by weight of core pellets
II	Wax coating	
	cetostearyl alcohol	2.5 % by weight of core pellets
III	Polymer coating	
	Eudragit NE 30 D (dry)	15% by weight of pellets with first coating
	talc	50% by weight of dry polymer

The following dissolution profiles are observed using USP Apparatus 1 at 100 rpm in purified water at 37°C.

	Cumulative amount dissolved (%)		
Time (hours)	EFFEXOR ER	Formulation of Example 3	Dissolution range in %
2	14	8	< 30
4	40	32	30 to 55
8	67	68	56 to 80
12	79	85	65 to 90
24	93	98	> 80

The principal advantages of the pellets and compositions of the present invention include a release profile of venlafaxine as effective as the commercially available product, however without the use of an organic solvent medium at least for application of the second coating. A further advantage is the absence of any organic solvent residue in the coated pellets.

The process is more cost-effective and less harzardous than hitherto known processes.

The coated pellets of this invention are thus produced using more economically and environmentally attractive processes than hitherto known processes for venlafaxine.

Claims

1. A coated pellet comprising

a) a pellet core which comprises venlafaxine hydrochloride;

b) a first coating which comprises a lipophilic layer or a sparingly water-soluble layer, and

c) a second coating which comprises a water-insoluble polymer or polymer mixture.

2. A pellet as claimed in claim 1 wherein the core additionally comprises a carrier, e.g. microcrystalline cellulose.

3. A pellet as claimed in claim 1 or claim 2 wherein the core further comprises a binder.

4. A pellet as claimed in claim 3 wherein the binder comprises a cellulose derivative.

5. A pellet as claimed in claim 3 or claim 4 wherein the binder comprises hydroxypropyl methylcellulose (HPMC).

6. A pellet as claimed in claim 1 or claim 2 wherein the lipophilic layer comprises a fat, fatty alcohol or wax.

7. A pellet as claimed in any preceding claim wherein the lipophilic layer comprises cetostearyl alcohol, castor oil or dibutyl phthalate.

8. A pellet as claimed in claim 1 or claim 2 wherein the sparingly water-soluble layer comprises a sugar, e.g. lactose, in the form of an aqueous suspension wherein the concentration of the sugar is at least 0.3 g/ml.

9. A pellet as claimed in any preceding claim wherein the water-insoluble polymer is selected from polymethacrylate dispersions, ethylcellulose dispersions and polyvinyl acetate dispersions.

10. A composition comprising pellets as claimed in any preceding claim.

11. A composition as claimed in claim 10 in tablet, hard gelatine capsule or sachet form.

12. A process for preparing coated pellet cores which process comprises the steps of

i) forming a pellet core mixture comprising venlafaxine hydrochloride with water or an aqueous solution of a binder,

ii) extruding and spheronising the mixture, drying and sieving,

iii) applying a first coating, and

iv) applying a second coating,

wherein the process is carried out in the absence or substantial absence of any organic solvent medium at least in the second coating.

13. A process as claimed in claim 12 wherein the pellet core mixture further comprises microcrystalline cellulose and HPMC.

14. A process as claimed in claim 12 or claim 13 wherein the process is carried out in the absence or substantial absence of any organic solvent medium in both the first and second coatings.

15. A coated pellet produced by the process as claimed in any one of claims 12 to 14.

16. A pellet, composition or process substantially as herein described with particular reference to the Examples.